

Transcript

**Fourth Meeting of the  
Secretary's Advisory Committee on Xenotransplantation,  
U.S. Department of Health and Human Services**

Tuesday, March 12, 2002

Breakout Session: SACX Working Group on Informed Consent Issues

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**Agenda Item: Breakout Session, SACX Working Group on Informed Consent Issues**

**DR. VANDERPOOL:** I think we should proceed. And our format is, you saw in the e-mail from Mary, is to follow the outline of, first off, the definitions of informed consent, and then components and characteristics of the process, then topics critical to the consent form, then third-party consent, issues involving lifelong surveillance. And of course any other issue we feel we need to raise.

Now, in talking with Jon Nelson -- we're glad to have Jon with us from Health Resources and Services -- we'll want to talk toward the end about what we need to do with this report, what's politically feasible, what's politically necessary, because we are the secretary's committee. But instead of dealing with those issues now, which could end up complicating the substance of what we've been working on, let's just proceed with the substance, and then we will let those issues of expediency and so on affect us as they will down the line.

Now, what you have before you, let's move now to definitions of informed consent. What you have before you in terms of 9 March 2000 has the initial document that I sent to Lilly, with Lilly's comments or suggestions in italics. And what I did was I re -- I will go ahead and hand you out a new copy of what I did. I actually revised the copy I sent to Lilly, and don't -- you don't have to deal with this now, but it's a more polished version of what I sent to her. And what I intended for Lilly and my work to be would be a suggested title for our paper, study, a suggested introduction, and a suggested first section on informed consent. And we call this definition informed consent but Lilly and I think agree it should be called ethical foundations and functions of informed consent.

Why don't we simply read through what we have before us with a March 9 date from Lilly and then entertain comments or corrections. We sought to define informed consent and to introduce -- what I did in the introduction was to seek to set informed consent within the framework of the mini-ethical issues. So let's just read through this, take a few minutes, and then discuss it. The March 9 written across the top is the one with Lilly's suggested changes and additions.

**MR. PHELPS:** The one that just came around says March 2002.

**DR. VANDERPOOL:** That's my redone statement. I sent one to Lilly and this is the one she's changed. My redone statement, set aside, but it changes some things that are in nonitalicized lettering. I didn't add a lot. Okay. Do you see what I'm saying, Paul? The March 2000 is my statement, okay, that I revised. What we have before us is Lilly's and mine input without my revisions.

**MR. PHELPS:** Okay. Labeled defense Exhibit B.

**DR. VANDERPOOL:** As with last time, I'll be putting a few things on the flip charts as we go along. It seems to me that what we should do with each of these topics is to ask if there are any major considerations that we have with what we're presented, particularly when we have something written out like this, and deal with those, if there are such, but we don't need to micromanage. I think what both Lilly and I both would welcome is whatever corrections, deletions you would have, if they are important ones, let's talk about them. If there are important substantive issues to raise, then by all means, let's start raising them now. The desire was to have an introduction, and then this first section on the ethical foundations and functions of informed consent, quite obviously embedded within the discussion that you see from myself and Lilly, is something about process, the next section. Process meaning that process has to accord with certain functions, information, exchange, comprehension and full volunteerism. So there are going to be some things that the process group can pick up from this or could even begin with the idea that embedded within the previous discussion is the notion that consent must include several elements. And the process of consent seeks to expand upon and make these clearer, and further define what the consent is.

So without any further comments, what do you think? And do you have suggested changes you think ought to be made?

**DR. RUSSOW:** I have cleaned up the grammar by the way.

**MR. BERGER:** Let me ask you a question. This particular section, what is its purpose of being used? I mean, will this be -- if we draft an informed consent document, is this the introductory part of it, or is it just to introduce the topic as part of a report?

**DR. VANDERPOOL:** This would be the introductory part as I would envision it, but we don't have to agree with that. The reason why we presented it the way it is, we wanted to embed informed consent within the broader framework of ethical issues pertaining to xenotransplantation. There's no way we can deal with all of these, but we do want to work on informed consent because they are important and unique issues here.

**MR. BERGER:** For instance, if there was, which we are looking at a draft of the things that should go into an informed consent statement, this might be the introduction of that that might be used as a guideline for potentially some medical centers, like Duke, for instance, that might look at something like this. And I'm only bringing this up, and if so, the thing that I think that's not necessarily missing, but needs to be really expanded upon, the one thing that makes this dramatically different about xenotransplantation is the third-party risk. And it should be really expanded in this

because anyone that may look at an informed consent statement, again, the theme that's different, that they may be entering into a clinical trial that has repercussions way beyond their own personal situation. And it should be highlighted even more in this along with being part of this statement. That's just my own opinion.

**DR. CRONE:** One possibility of doing that would be somewhere in a section like this, just reading your revised one, Harold, would be somewhere to put in a section in here, and also because of some of Lilly's comments which add into these comments about -- that are unique to xenotransplantation, is that this sort of coverage and overall about informed consent. It may be helpful for there to be a section, a separate section built in here that says there are issues particular to xenotransplantation, why, you know -- particularly informed consent, there's going to be certain issues that are going to be unusual.

**MS. KING:** They do have that, but you're saying expound upon that?

**DR. CRONE:** I think, you know, it's like an underlying section, so I can read here and go -- because otherwise I can read here and go okay, this is informed consent, okay. But I can look particularly and say okay, well, what's unique to this. Why even put this out, why even have this.

**DR. VANDERPOOL:** Okay. So your suggestion is to highlight within the general discussion of the consent the unique issues?

**DR. CRONE:** Yeah.

**DR. VANDERPOOL:** Should you do that in terms of, first of all, just giving a brief discussion and then say -- have a separate section on unique issues related to xenotransplantation? Or should you weave those into --

**DR. CRONE:** I wasn't thinking about weaving it in, because I'm thinking of it being nice and direct and, you know, that somebody doesn't just sit there and sort of glaze over. Because some people are going to read it and are going to be very familiar with informed consent issues. What they are going to want to know is why is this in particular, why are we so concerned with xenotransplant.

**DR. VANDERPOOL:** So you're saying the first is just a general intro of a lot of issues. Just some very brief discussion. And then the next issue would be issues that are unique to xeno. And then we go to the issues of process and consent form and so on? I like that.

**MR. NELSON:** That's a good format. Maybe explain it to me a little better. One of the unique features of this is the fact you've got a third party, but they are not at the

table. If you're talking about an informed consent document, you're not getting informed consent from the general population that Alan or I should receive a tissue transplant from another species.

**MR. BERGER:** I won't do that by the way. I can probably go on record and --

**MR. NELSON:** But the issue is, I mean, there's a third party here but they are hardly at the table and they are not part of the consent process, so it devolves back to the original pair where in Solary (?) transplantation a donor and a recipient --

**DR. CRONE:** See, I don't think it's just that issue of this. I mean, I think what's unique -- I think some of the things that are unique, that is a part of it. The things that are unique are there are some unusual risks because we don't know about some of the infectious risks that are potentially there. That's like a real unknown. It's not like you can say with an operation, well, you know, you might have postop bleeding, you may have certain infections, you may have -- you know, they are very certain, defined things. And also the fact that you're talking about long term, really long term monitoring, because you might become a health risk.

**MR. FINN:** Is there such a thing as presumed public consent?

**MS. SHAPIRO:** See, I think that this issue is part of the informed consent process, because in the informed consent process we are going to be asking them to involve, at least educate or inform in a closed context. That's part of the informed consent to participants, just as the lifelong monitoring request is.

**DR. BLOOM:** A lot of this is laid out in -- never mind.

**DR. VANDERPOOL:** What we may want to do in terms of identifying these unique areas, I like what Catherine has said about making a separate section, unique risk, unique responsibilities that go with being a patient. Namely, to see that your intimate contacts are educated and so on. Technically, they can't give informed consent for the procedure. May be something we need to hammer out. But unique risks, unique responsibilities and lifelong surveillance, which will affect questions of not being able or being able to withdraw at any time. So I do think it's good to really highlight the unique features.

And what Brad and Alan and I did is to develop a fairly lengthy statement on what all needs to be on a consent form. And this -- maybe we should deal with that. Look at this right now and star the things that are unique that come through with what needs to be on a consent form, and then talk about process after we get through with this question of whether the categories that are unique and so on.

Now, this is our -- this is our document, and I'll walk us through it.

**MS. KING:** Harold, I need to add something while I'm thinking about it. I had the same thought Catherine had. I don't think it's just unusual risks, it's unknown risk. We are asking people to sign informed consent, and it's really unknown risk, so they really -- it's rather contradictory. It's unusual because it's because we don't know, which makes it unique.

**DR. VANDERPOOL:** Yeah, it's unique because it's unknown. Good. Other comments about -- Lilly.

**DR. RUSSOW:** Yeah. I'd like to get back to Alan's question. That is to say, are we going to try to take this, that is, the original statement, and sort of build the rest of these concerns that haven't been addressed yet into it, or is this going to be the introduction into other sections?

**DR. VANDERPOOL:** It seems to me what we need to do is just get straight out what informed consent is, and then say what's unique about this for xeno, and then go to perhaps the contents of the consent form and the consent process and so on.

**DR. RUSSOW:** I guess my question was sort of more specific in terms of the format. That is to say, should we take this as, you know, as amended, but basically keeping it in the same shape as an introduction, and then add all of those as separate sections following this? Or should we just try to take this and expand upon it internally?

**DR. VANDERPOOL:** I think we need -- what do you think? To me it needs to be a separate section. We need to have a good, clear, well-documented statement on what informed consent is about. And then you move to the things that are unique to xeno and then that would lead to a separate section on what's unique, and lead to a separate section on a suggested outline for consent form, and suggested things about the consent process. When you talk about the unique sections, some of that is going to end up needing to be discussed in the separate section. For example, under lifelong surveillance, how do we deal with this legally and ethically.

**DR. CRONE:** I think that, Lilly, in kind of looking, I just had a chance to read yours earlier, so I read Harold's revised ones. I think a lot of the comments you made, a lot of the add-ons are some things that will probably end up under --

**DR. VANDERPOOL:** Under two.

**DR. CRONE:** -- under the process because you bring up a lot of points.

**DR. RUSSOW:** Actually, it would belong a little bit to two and to the unique characteristics and the process, so, just pull those out and develop.

**DR. CRONE:** I think one of the things that I had felt with this is that the way it's done, you're bringing up points that are very valid, but it's going to get lost in the rest of the discussion about informed consent in general. And I think we want to say something particular in regards to xenotransplant.

**DR. VANDERPOOL:** What we're looking at is this brief introduction, a brief statement of IC, without too many -- informed consent without too many things about the third section on unique informed consent issues to xenotransplantation, followed by the content of forms, followed by things about the process, and then followed by sections on further discussion of some of the issues that are highlighted here about unique issues and what to do with them. Does that make sense as an outline?

**MR. PHELPS:** Tactically it's a very good way to structure the paper. It states the structure, narrows the focus to xeno. Deals with the unique issues one by one. In terms of the form and process you've got a recapitulation at the end. My only criticism is that you've got two introductions now. That's a lot of foreplay. Perhaps you need an executive summary at the beginning of it, but I don't think you need an introduction beyond the opening statement on informed consent. Informed consent is an important process, here's the history of it, here's what's special about informed consent in xenotransplantation. You might want a sentence who the committee is and why you're looking at this, who asked you to look at it. But beyond that you don't need any further introduction.

**DR. VANDERPOOL:** You don't think we need to say something about the broader issues, ethical issues surrounding xeno, and informed consent is a critical issue within this area?

**MR. PHELPS:** Other than to say there are broader ethical issues and this particular paper deals with the issue of informed consent. Again, it's a narrowing down of the focus to the subject that you're actually going to address.

**DR. VANDERPOOL:** Right.

**MR. PHELPS:** Quickly as you can get there.

**DR. VANDERPOOL:** Well, you're right. That's why in my initial draft I only took two paragraphs there. The reason why I thought it was important to talk about the other issues is that almost all the other discussions focus on -- they do a laundry list approach to the problems in xeno. And it's good to say, yeah, okay, there's a laundry list, and here are what they are. But our committee feels that we really need to focus on informed -- one of these issues at a time, and this is xeno. If we can abbreviate that further.

**MR. PHELPS:** If you can do it in a paragraph or two, that's all the warming up that you really need before you move to informed consent.

**DR. VANDERPOOL:** We have only two paragraphs. We can look for even more abbreviations. Lilly.

**DR. RUSSOW:** Yeah. I just wanted to say that I think it's important to have some sort of thing like the one that you have in the second and third paragraphs, just to say, we're not ignoring these, they are also very important issues, but we're focusing on informed consent. And we might even add a sentence about why we're focusing on informed consent in terms of its immediacy, the fact that clinical trials are being planned right now. And so it has immediate and concrete issue. Again, that would be part of the intro, just part of the narrowing down, but I think it needs to be there, because otherwise people are going to read it and say, wait a second, they don't talk about justice at all, how can that be. So I think we need to explain why we've chosen informed consent as our particular focus.

The other thing that I was going to suggest was that I like the outline very much, but I was thinking that it would make more sense to switch four and five, that is, content and process. Because I think in effect you need to talk about the process first, what it is that you're trying to accomplish, and where you're going before you can define the content.

**DR. VANDERPOOL:** That was our initial outline, so that certainly makes sense. The reason why I wanted to hand out the process, and then let's talk about later, is to indicate that we're talking about the Section 4 on Page 2, responsibilities, that's unique. See, that's really unique. And then under risk, there are going to be some unique things there. Discomforts in quality of life. And then Section 10 on Page 5 is certainly unique and I went ahead -- you know how shy I am anyway. I do this for heuristic reasons, not in order to be authoritarian, I'm serious about. You know me. But for heuristic reasons, I went ahead and put in some kind of wording in number 10, this issued that voluntary -- and this was also suggested by Brad to me and part of his wording is in here -- voluntary enrollment accompanied by prohibitions against or limitations against withdrawal. And I mean, that's unique also.

And so this outline, we've tried to draw together all the essential elements. Now, what we might want to do is get rid of some of them and say some of them are not needed. As I say under sources, I say, well, these are the sources that have been used to put this outline together. Well, one of the notable things is we only have one protocol to go off of, and we're getting more, thankfully, as examples, and those will be truly confidential protocols. We can't talk about these to the public or speak about them here but they will be important for us to be able to get perspective on what these forms are like. Are they full of numbing detail. Do they cover the issues well enough.



So let's put this on hold. What I'm saying is -- the reason why I was handing this out is because the content of the consent form document that we've prepared for you does flag the unique issues. And I can entirely agree that these need to be brought right up front as unique issues early in the essay, and then later on under both process and consent forms, these are expanded on in terms of specifics. Any comments or questions?  
Robyn.

**MS. SHAPIRO:** Yeah. And I don't know where we want to go in terms of how we're planning the discussion today, but I am going to -- we're going to have a problem with the responsibilities section and also the voluntary enrollment accompanied by prohibitions against withdrawal section. So substantively I think we have a lot of work to do on that.

**DR. VANDERPOOL:** Exactly. I completely agree.

**MS. SHAPIRO:** I think it's going to end up, legally speaking, looking more like we're going to ask you, and if we don't, the wrath of the public health system could be brought to bear, and you should know about that, that's part of the informed consent. But to prohibit them from being able to withdraw, it's just not going to work.

The second thing is I think that the community consent needs to be a separate section. That's not really informed consent of the research participants but it's important. So can we broaden our mission here to include not just informed consent but also the notion of community involvement?

**DR. VANDERPOOL:** I almost think that's a separate paper.

**MS. SHAPIRO:** It might be, but we --

**DR. VANDERPOOL:** We're talking about informed consent for the prospective subjects.

**MS. SHAPIRO:** It is, but in the context of, if you look at the federal regulations now, and I spoke with someone whose name I'm blanking at the moment, Bonnie Lee, who had suggested about this community consent thing, that we look at the Emergency Research Exception, which is exactly what I have put down in my outline going way back when. It's part of launching a trial though, hopefully before you would do all of this. So a sense of urgency about why we're dealing with informed consent now, because we're maybe on the cusp of trials and that kind of thing. I think we need to get that out there. It's part of the bigger environment of informed consent.

**DR. BLOOM:** I strongly second what Robyn just said. I think it's important at this

point, even if you don't have a plan for community involvement, that it's an important issue and we are working on it, we're going to develop some means to do that.

I would also suggest, and just looking at the top line, that we've been provided, Harold, maybe you don't want to talk about this now, I would suggest putting risks before responsibilities, because the responsibilities become a lot more understandable in the context of what the risks are. And some of the things that you have under risks, like the bearing of these risks on subject's behavior, sexual relations, intimate contacts, those are actually responsibilities. Those are just picky comments.

But I'd also suggest that you look at FDA's guidance, where we have an outline of what kinds of items should be in the informed consent too. They are consistent with the PHS, but worded slightly differently and organized slightly differently and it might be helpful.

**DR. VANDERPOOL:** Excellent. These are all tentative documents and I think your suggestions are all very important. I mean, for example, one of the things Brad mentioned under the consent form is that under Section 2, nature and purpose, Page 2, Brad suggested that alternative treatments be brought up front. Usually these are tail end discussions on consent forms, and before IRBs, but I thought that 2D, alternative treatment, should be brought up forward, because in order for patients to know really what their options are as they -- and take them seriously as they consider participation.

And I think Eda's suggestion is also right on target, that risks ought to precede responsibilities, because risk are the things that make the responsibilities make sense. So that's definitely a fine suggestion. Alan.

**MR. BERGER:** Harold, I had two questions. One is, and this was one of my interest about the community, what is the procedure if in fact a medical center is working with infectious diseases, to the community Public Health Service, the city that you're operating in? In fact, if you're doing an operation that may have broader public health problems, do you need to contact the city you're working in and contact public health? Do they need to be advised? Should we be doing something that would advise? It's outside of this document, which frankly brings me to a second question.

We've been centering on informed consent, but as I recall, this was set up to try and put everything focused that we're looking at outside of the science in an informed consent umbrella, and as was just pointed out, it doesn't seem to all fit there. There may be other topics separate to this that we want to separate out. My own opinion is the whole surveillance that we're doing is not adequate, including having voluntary approaches, which in my opinion doesn't work and doesn't really protect the public and makes this difficult to do.

**MS. SHAPIRO:** Well, again, just to kind of clarify what I said. We do have public

health laws throughout the country that hopefully will be poised to be brought to bear if there's not voluntary cooperation and we perceive a risk.

The other thing that I was wondering, if we wanted to -- since this is unusual, what I'd like to see included somewhere in here is some suggestions for research on people who have and will participate. What is the impact of this new, almost requirement, but not really, to undergo all this lifelong this, that and the other thing. To be able to have the benefit, which we do of Jim, about how that's affecting people, and whether it's working, and so that we can continue to refine our approach to this, which, you know we're doing our best at it at the moment.

**DR. VANDERPOOL:** When I called -- I was asked by Mary to call Mike Carome (phonetic), who is head of the Office for Human Resource Protections. And Mike and I had a very long conversation over the phone about third-party consent. And Robyn has been -- and your group has been working on this too, very important part of this entire subject. But Mike said -- we talked about two main things. For one thing, the name third-party consent is a bit confusing in terms of past usage. Third-party consent in terms of community genetic research regards all those people who are not immediately involved with the disease. So he was suggesting maybe third-party consent is going to be confusing for some people who read this, so you should talk about consent for intimate contacts, family members and say members of the community.

The second point he made was that at any point that we would wish we could -- on any research protocol you can always go to the Secretary of the DHHS for exceptions. And so you might want to go to the Secretary for a permissible exception to the notion of being able to withdraw at any time. That this would be permissible when risks are the way they are here. But he was suggesting the process for doing that would be to go to the Secretary for the exception.

**DR. CRONE:** I think that there would be a need to have new regulations, which -- and I'm not so sure, since I do think that we have this umbrella of the public health system available, I'm not so sure I think that's a war we need to fight.

**MR. BERGER:** Maybe I'd like some clarification. I mean, I live in the San Francisco area, I know it's not a voluntary research area, you have ACT UP in San Francisco, which is proposing all over town that people that are HIV positive have safe sex, and I don't see the Public Health Service doing anything, nor do I see anyone arrested, nor do I see anything happening, and that's certainly a public health risk. So I'm very curious exactly what the Public Health Service can actually do from a legal point of view to enforce people to comply with regulations or to comply with an informed consent guideline.

**MS. SHAPIRO:** The public health system is not about to go and jail the ACT UP

people. On the other hand, it's not just public health, and I've seen this in Milwaukee, it's the district attorney who will prosecute individuals who insist on being unsafe if they are HIV infected. So you need to -- I mean, yes, you need to identify the individual or the problem, but I think we're talking about two different things here.

**DR. VANDERPOOL:** It strikes me that in terms of -- that there is a lot about community consent going on, and Fischbach is one of the leading advocates of community consent, and he likens community consent to patient informed consent, which may not be parallel. But you can either go in the direction of finding some means to get a community to consent to this risky research that's going on in the university nearby, although given the travel in the United States you might need the consent from the entire U.S. public if you press the issue, and then how in the world would you do that.

Rather than taking that approach, the way I've read it over time is, primarily through the FDA and the Center for Disease Control and so on, you make sure that the risk are minimized where the community is protected in all reasonable levels. Now, to protect the community, either you go -- consider the community which presumably would need, according to Fishbach to say, oh, we'd be happy to have this minority of people have xenotransplant operations, even though it puts us all at risk. That's easily subject to abuse. Those kind of worries and so on, special interest groups. Instead of community consent, then the question would be, is the public being protected well enough for us to really be responsible about the risk involved.

Now, that may lead to what Brad talked about at our last meeting, and that is, should you do psychological testing of patients or examinations to make sure that, insofar as you can be sure, that these people will be the ones who are willing to be monitored and on a lifelong level. Now that raises a tricky issue. But if they are desperate patients, they may say yes anyway, regardless of what they plan to do when they get the transplants.

**MR. NELSON:** Issues of compliance are normally on the table anyway, for most transplant patients, because it's part of the medical workup. You want to know whether it's xenotransplantation or whether it's another form of transplantation if they are going to comply with the regimen that's necessary for them to survive. And in this case, necessary to protect the broader public's health, so.

**MS. SHAPIRO:** Here is an example of how it could work out. They are scheduled for this follow-up and they are going to be scheduled for follow-up for their lifetime and they don't show up, and the doctor then picks up the phone and calls the public health official who will take appropriate action. We'll go to the house, we'll send a letter, we'll start a lawsuit, we'll quarantine, whatever it is that seems given the state of the science that we know at that moment is indicated.

**MR. BERGER:** But what do they do to a third party, for instance, a loved one, a lover, a relationship that's broken up. Even if they are going out and doing unsafe sex, they don't need to report it to the medical center, and they probably aren't going to --

**MS. SHAPIRO:** Well, wait, so you want cameras in the bedroom now? I mean, where are you going with this?

**MR. BERGER:** Well, you have risks and you have risks to certain procedures that they follow. You have risk to third parties that aren't part of the informed consent, right? That's what we've been talking about.

**MS. SHAPIRO:** No, it would be. The education and the information would be part of the informed consent.

**MR. BERGER:** I mean, they are not signing a document.

**MS. SHAPIRO:** Right. Third party or whatever you want to call them, they are not the patient.

**MR. BERGER:** The spouse of the patient, as Brad pointed out, they might be part of and they will be part of the actual interview process, but you're way beyond the patient themselves. Or, if the patient moves, Harold was just talking, we are a transient population. And all that I am saying is that I don't see where we have adequate surveillance to be able to really monitor or make it really a mandatory process.

**MS. SHAPIRO:** We don't, and I don't know that we would want it, if it's cameras in the bedroom.

**MR. BERGER:** Well, I'm not asking for that exactly.

**MS. SHAPIRO:** But conceivably I mean, it's endless. You know, this one sleeps with this one, and then that one then, you know, shares a toothbrush with that one, and you know, I mean --

**MR. BERGER:** But we are knowingly, I mean, this committee in a more general sense, is knowingly or may be knowingly approving or recommending a medical procedure that may have larger infectious disease risk. So the committee is knowingly doing that, so there are risks for the general public. And everyone, all of us have to assess for ourselves whether their surveillance is adequate to cover that kind of risk. And I'm exploring that, as to whether there are procedures in place to be able to protect the public better.

**DR. VANDERPOOL:** Those are important issues. We also knowingly do things all

the time from everything from genetically engineered foods, to driving our automobiles, to setting speed limits, to allowing people to buy salted Fritos in any quantity they wish to eat, and not monitoring via the government weight gain and so on. We have these -- we knowingly have a lot of things going on. It is important for us to assess whether the possible risks of xeno to the public are great enough to take stronger actions than other public risks that we face day after day. That is a struggle we need to have. Jon.

**MR. NELSON:** I think you're struggling with trying to convey to the patient their responsibility to understand the risk and be able to make an informed consent for the broader public, and I don't think we can do that. I think you have to put their decision-making process in the context of what the implications are for the broader population, but not that they are ultimately responsible for that, because they are not. They are looking out for their own best interest and arguably for their immediate family members.

**DR. VANDERPOOL:** And let them know about their immediate family members especially.

**MR. NELSON:** You say what the risk is of the population, I think that's a fundamental responsibility. But this broader group has to decide, and also individual transplant programs, what the risks are for the population.

**DR. VANDERPOOL:** And vis-à-vis that, Jon, on Page 3 of the informed consent outline, where we try to capture some of the contact, we said lifelong health surveillance, regular checkups, et cetera, education of family members, close contact regarding infectious disease, risk willing to give blood specimen, do follow-up precautionary measures, report any unexplained illnesses. This should be accompanied by assurances that counselor or members of the team will research participants with these responsibilities. So that there is this educational component that has to follow, but that's not only what -- I mean, I remember when the first guidelines came out, Public Service Guidelines, and I was asked for a commentary, and one of my first commentaries was you've put all this education on the back of the participant who is often -- whose health is often incredibly compromised, so this has to be done with counseling and other things. Lilly, did you have --

**DR. RUSSOW:** Yeah, it strikes me that -- it's obvious this whole issue of community impact and third parties being involved is incredibly important. But I think that we're trying to lump too much together. That is to say, I think that they are separate issues. One is the involvement of, let's call them intimate contacts, although you're right that that can change from moment to moment. At least we can try to identify the intimate contacts right now at the time of the informed consent. And they obviously ought to play an active role in the decision, recognize what they are getting themselves into. How we deal with that is a separate issue, but that's one category.

The second category that people were worried about, and I think Alan's example is a good one, is patients or participants who knowingly act recklessly, that is to say, you know, if you've been diagnosed with HIV, presumably part of what you are told is that unprotected sex, you know, puts others at risk. And I think that an informed consent form, right now it has it implicitly, but explicitly here is behavior that might put others at risk, and therefore you either need to refrain from them, like donating blood, or just be very careful about making sure that this fits in with your approved and recommended lifestyle, whatever you want to call it.

And then the third category would be the community at large, and we've got several precedents for that in the past. The one thing that comes to mind is the debate in Cambridge, Massachusetts about what was then called recombinant DNA research, and there was in fact a big community discussion about whether we want -- they want laboratories to pursue that sort of research. And as far as I can see, that the way that that has been handled, which seems to work fairly well, is that as long as the public is justified in believing that -- justified in having faith in the procedures like the Public Health Service and other responsibilities, as long as they are convinced or can be convinced that those oversight committees or organizations are doing their job properly, that may be all that's necessary. That certainly has been the case with other kinds of potential risks. And yeah, you are going to have always the Jeremy Rifkins of the world who are just not going to be satisfied with anything except total stoppage. But if there are reasonable questions about, hey, you know, is the Public Health Service or whatever really looking after the community interests, or are they just sitting back and waiting for a disaster to happen so that they can clean up after it. As long as the community doesn't have any reason to doubt the efficacy and the reliability of those kinds of checks and balances, that would seem to be the way that community impact in general has been handled and, you know, it seems to be working fairly well. But I think it's important to distinguish those three kinds of categories so that we can get clear. Because some of the things apply to one but not the other and --

**DR. VANDERPOOL:** Lilly, a question. I like your categories. Intimate contact, patients who just knowingly would act recklessly in the community at large. Do you think that what we are wanting to do here should address the community at large issue or mention it, but not try to work it out or what?

**DR. RUSSOW:** I think we definitely need to recognize it as an important component. It may --

**DR. VANDERPOOL:** Not necessarily an informed consent.

**DR. RUSSOW:** Right, it wouldn't be, but it would be recognizing that the community at large has an interest in all of this. And I don't know how much detail we want to go

into about how that gets addressed. We might just want to point to previous cases like, at that point, recombinant DNA, and say this is a precedent, we should consider that as, you know, at least a starting point. I don't think we can solve the whole issue of community involvement or community impact, but I think it needs to be acknowledged.

**MS. SHAPIRO:** And again, regulatory-wise, we do have a special regulatory provision about emergency consents, and what it addresses is you can't consent at the moment to research because you're in an emergency, but we want to try to promote that so that if a hospital wants to do that in their ER they have to have certain kind of educational programming. It's more like informing. And I think that that's some place that we should go to, that we should think about that falling within that.

**DR. VANDERPOOL:** Since we're dealing with issues, Robyn, you and others have talked about this more, let's go ahead and have that discussion now. We'll go back to the process of consent when it's time to do that, but let's go ahead and proceed with this issue of third-party consent, quote, third-party consent, community consent and issues involving -- also the obligations or responsibilities of subjects to do certain things to protect their intimate contacts and to protect the public by, for example, lifelong surveillance.

**MR. PHELPS:** I have a naive question, sometimes they are the best kind. The purpose of informed consent is to protect the subject of research from harm. I don't understand how informed consent from the community, although it's a valid concern, is part of this process. Why is that being yoked with the protection of the individual subject? If there's a need to inform the community and get the community's consent, the responsibility for that, it seems to me, falls to the researchers or to the institution where they are doing their research, the way NIH needs to inform its community that there's research on drug resistant TB going on on campus, and if the community howled loud enough, maybe they stopped doing it, as I think they stopped incinerating medicinal waste.

**MS. SHAPIRO:** That's why I suggested that it is a separate section, but it's an important separate section.

**MR. PHELPS:** Does it belong in this paper or is it a separate paper?

**MS. SHAPIRO:** It's a separate paper under the rubric of consent if we didn't call it informed consent of participant. If it's consent, it would fit nicely within that paper. Even if it's a separate paper, I think that it's an important prelude to any clinical trial or any thought of proceeding along those lines, as much as is having a good informed consent document.

**DR. VANDERPOOL:** Dr. Collins. Brad.



**DR. COLLINS:** Thanks, Harold. I just want to say a part of that community consent in informing the community is a protection for the subject. If the subject can't consent, as Robyn was mentioning, in the emergency department, comatose and the university goes ahead and does what needs to be done to save the patient's life, the community needs to be informed that that can take place there and that's seen as a protection. Other scientists in the community can say, well, if that ever happens again you shouldn't do it because it leads to this. It's just a part of protecting the subjects who appear and can't protect themselves.

**MS. SHAPIRO:** Because it could be them tomorrow?

**DR. COLLINS:** Right.

**DR. VANDERPOOL:** The other addition to that is you're right, key issue of informed consent is to protect the subject, but if what the subject is consenting to do puts the community at a possible risk or conceivable risk, then the subject can't be seen as merely operating in this separate world on her or his own, but is ipso facto bringing the community into the risk ratio. I mean, those are the arguments that Fishbach and others are using.

As I say, one can either try to go the route of community consent whatever in the world -- however in the world that might ever be done, usually done in democracy through elected representatives and not through interest groups alone. But rather than do that our usual procedure has been to have good public health provisions in place to protect the community. Now, if at some point the community becomes alarmed enough to think it's not being protected, then what we've said about that, at that point, you know, pardon my Latin, all hell breaks loose anyway and you have to go back and almost renegotiate the covenant with the public. Other comments? Alan

**MR. BERGER:** This is where I do agree with you Robyn. What I was actually trying to bring up earlier and probably didn't really articulate it well, I do think there may be one or two or three other topics that don't fit into an informed consent document. I certainly didn't indicate that we should have some kind of community consent within this document. It should be much cleaner, although certainly the patient should be informed very clearly about risks well beyond that person.

But we may want to identify one or two or three other topics similar to this that we want to make a statement, maybe not a paper per se, but a statement that's broader than or outside of this particular document. That's really where I had heading before.

**DR. VANDERPOOL:** And this issue of community is a big area, and I think to make

a statement about this would presume our doing a good bit of research. I think Lilly's very articulate statement about Cambridge, Mass and the recombinant DNA, I happened to be a student at the time, and when the mayor of Cambridge said no, you can't build that lab over there because there was all this furor of E. coli getting out and running down the streets of Cambridge. So it didn't occur but there was certainly concerns about it. Eda.

**DR. BLOOM:** I think what you're talking about is not community consent, but community education and involvement, and I'd be careful to cache it like that.

**DR. VANDERPOOL:** Exactly, precisely. We probably should drop the word community consent.

**DR. RUSSOW:** I agree with that, but I get kind of worried when I hear people talking about the need to educate the community, because while in and of itself it sounds like exactly the right sort of thing to do, what I hear from the scientific community fairly frequently is, oh, the public is just ignorant, and if they knew that we were responsible, there wouldn't be a problem. I hear that particularly with animal research. You know, the scientists just say, well, that's because the public doesn't understand the way science needs to be done. To some extent that's true, and education is important. But it's not like the general public is a bunch of dummies. They have legitimate concerns that may not be of primary, right at the forefront of the scientific researcher's mind. And so I think, yes, education is the right way to go, but we ought not to use that to kind of dismiss public concerns in general, which sometimes seems to happen, at least that's the presumption in a lot of cases.

**DR. BLOOM:** That's why the term involvement, also.

**MS. KING:** I would suggest that it's not enough to even say community education and involvement, whose responsibility is that. Because if it's not spelled out that there are some responsibilities among whomever, be it the institutions who are conducting or whatever, it won't happen.

**DR. VANDERPOOL:** That's really very important, because even though that's not our topic, community education involvement is an issue, we need to point to it as an auxiliary concern that will be dealt with or needs to be dealt with in and of itself.

You know, community consent is one of those phrases that I don't believe is sensible, but it's one of those phrases, sort of like death with dignity, it just won't go away because it sounds -- cc, community consent. I think people are going to continue to talk about death with dignity. I wrote a whole article for JAMA, hundreds of requests for it, how death was not death with dignity, let's talk about death in terms of having degrees of human worth. It's not a dignifying thing. Death with dignity didn't make any sense,

but we still use it. It's just a phrase to use. So community consent is probably still going to haunt us even though we say that's not really what's going on.

**MS. KING:** Harold, on the consent form itself, too, I would suggest that the education of family should be a separate point just like the community education, because to me that doesn't really fit in an informed consent document. Because, again, we were saying it's not just the patient's responsibility, it's the institution's responsibility to work with that patient to -- the patient needs to say who should be educated, but I think to leave it to the patient -- as Jim said, when he read that document he couldn't have gone off and now educated your family about what was in the document, because you didn't read it that closely because you knew you wanted the procedure. So I would suggest that that should maybe be alluded to in the document, but I think detailed, it should be pulled out as a separate piece as well because of the importance of that, and the responsibility of the institution.

**DR. BLOOM:** The patient has to consent to their family being educated.

**MS. KING:** Right. So I think that should be mentioned in here. But I think that should be a standalone piece as to the importance of the facility or whomever in that process of education of the family and what they should be educated about.

**DR. VANDERPOOL:** You can see on Page 3 I mentioned of it as -- I mean, that can be done in two sentences even though it's more spelled out. But you're right, it needs to be mentioned as one of the things that they consent to, is to know that their family members and close contacts need to be educated and have to abide by certain behaviors.

**MS. KING:** Probably would go in the process, actually, when we go into more detail.

**DR. BLOOM:** But the future, okay. This person may survive and with the xenotransplantation products we have right now we know they do. What about their intimate contacts next week or next month? I think they still have to be able to be prepared to talk to their intimate contacts and to educate them. They are not going to bring in their latest date or lover or toothbrush companion into their doctor.

**MS. KING:** I agree. I agree totally with that. I'm just saying I think it's important enough that it needs to be done. That probably would go under the process where we talk in more detail about the process of informed consent, that would be a piece of that.

**DR. VANDERPOOL:** What if we say you need to keep your toothbrush in a locked box. Let's quickly go through the consent form thing because it has lots of categories. Our challenge is -- for each of you to make suggestions about where categories need to be put. The huge challenge here is how to make this where disclosure can be comprehensive. You know, it needs to be comprehensive, okay. But the question

involved is how do you arrange this where it's the most easily comprehended and understood. And there's an attempt to do that here.

So the introduction would just be introductory statements, this is research and that you are urged to ask questions. Section E here could be a bit controversial. And that is sponsorship names affiliation's interest. This study is being funded by, which is paying and the such-and-such resource for conducting the study. This would be -- essentially represents a disclosure of conceivable conflicts of interest. That's being put increasingly on consent forms and IRB, and it seems to me to be sensible to have as an element in this one.

Nature and purpose, just to -- you can see these are the broad brushes, summary description of subject's diagnosis, condition, a brief summary of intention to use xenotransplant to deal with this condition. This is where you get morbidity and mortality information. This has been strongly urged by people like Charles McCarthy who wrote quite a lengthy article on informed consent in xeno some years ago.

Specific description of the purposes and then alternative treatments. As I said, Brad Collins said let's bring this forward so this is on the top of their neurons and not somewhere way back.

Then participants, brief statements of the number of participants, expected duration. It could be maybe participation rather than participants. Whether it be a control group inclusion and exclusion criteria.

Then I think the suggestion was from Eda to move the risk section up there. Let's don't deal with it there, but let's assume that's what we do.

Under responsibilities, participants in this research will be required to accept a number of future responsibilities. Now, Robyn needs to tear all these words to shred. But, Robyn, I tried to put it in there so it would be there. Will be required, will be urged, I mean --

**MS. SHAPIRO:** Expected.

**DR. VANDERPOOL:** Will be expected. Please, send all your such things. And these include lifelong surveillance, regular checkups, enlistment in databases and archives. Soon, Eda has told me that, we'll have a real monitoring system in place, certainly by clinical trials for organ transplant. It's coming along. Whatever that is or isn't needs to be state of the art at the time this is done, so if it's not in place it will be mentioned.

The duty of informing researchers of changing in address so on. Timely reporting of illnesses. No future blood donations, autopsy at the end of life.

Then education of family members and close contacts. This still focuses on what the responsibilities of the patients are, but they need to be assured that they will have

counselors and members of the research team. I think Karren you were exactly right, that this is really a hospital -- this is really a hospital responsibility, but they need to recognize that they are going to need to play a role in that.

Study procedures. At this point, the one consent form we had was 10 pages long. It seems to me this is where you get to the numbing detail that can just lead people, as Jim told us last time we were together, I didn't even read this thing until, you know, well after everything had been done. I had to rely on talking with people. So a lot of times there is incredible detail about we are going to give you these lab evaluations and test. First of all, you'll have to walk in the laboratory, then you'll have to take off your shirt, and then just on and on. And so I think this is an issue that we probably need to think of ways to urge clarity about what will happen, but also brevity in terms of description.

**DR. COLLINS:** I have a question for Robyn. Is that there to protect the investigators from future lawsuit, all that detail?

**MS. SHAPIRO:** Sure.

**DR. COLLINS:** Does it have to be there?

**MS. SHAPIRO:** Like any informed consent piece of paper, it's supposed to be evidence that if the subject comes back later and says, well, I never really knew this, you can pull this out and say, yeah, you did, don't you see. On the other hand, they can come back and say yeah, I was sedated at the time, or this was at a 12th grade reading level and I only have a fifth or you didn't really explain. That argument that you need all of that for that evidence doesn't do it for me.

**DR. COLLINS:** Okay.

**DR. VANDERPOOL:** But isn't Brad, right? I mean, on an IRB if you don't say we're taking 50 cc's of blood or 20 cc's of blood three times a day over the course of an afternoon and then someone happened to faint on -- after third 20 cc's were taken for whatever sets of reasons and they said, well, I didn't know that I'd be bled to death. Well, I mean, it's the lawyers on the committee who say, you know, we need this detail in there.

**MS. SHAPIRO:** That's why they shouldn't be on the committee. But the risk is that, yeah, that the patient is going to say I didn't know and had I known I would not have agreed. But, you know, the comeback to having it -- they can come back with that kind of argument even if you have a very detailed form. So it's not a be-all and end-all form of protection as some lawyers think it is.

**DR. COLLINS:** Okay.

**DR. VANDERPOOL:** Let me just make a -- and then Lilly and then Alan. One thing that occurred in the Diacrin consent form Jim gave us -- thank you, Jim, for being on our committee, that way we got a consent form without any manipulation. One of the things that could be done in that form, all the risks of immunosuppression were put in an appendix. And I think it would be possible for us to think about appendices for some of the detail. It wouldn't be appendices for the sake of the lawyers, it would be appendices. And that the institution will protect themselves, research protect themselves, for lawyers to be aware. So maybe that's what we need to think about. That if there are details here that the institution and their legal counsel feel needs to be there, but in terms of the process of consent and understanding complicates that, well, let's move it to appendices. That's one approach. Lilly and then Alan.

**DR. RUSSOW:** Yeah. I think you're absolutely right about lawyers, and that's why I stuck in that last, that last paragraph, because I really do think that, you know, as everybody has said, the primary purpose of an informed consent document is to protect the patient. That's the primary purpose. And if that secondary purpose, which is to kind of protect yourself against lawsuits, interferes with that primary purpose, it doesn't belong there. That sort of, you know, the CYA part of it, that's not really in the interest of the patient.

I think that Harold's suggestion about appendices is one way of dealing with this. Either in conjunction with appendices or some other form. The idea of a patient advocate who meets with the patient before the informed consent form is signed, you know, the patient has the form to look over, and it's the job of the patient advocate to make sure that if the patient has any questions or wants to know more about it, that they get that information from whatever source is most appropriate. But the job of the advocate, as I see it, is part of the team that discusses this before the patient naturally makes a decision. The job of the patient advocate is to make sure that questions that the patient himself might not ask, because they don't know enough to ask, you know, how many cc's of blood are you talking about here, that the job of the advocate is to say, look, are you comfortable with this, do you know what's involved, or do you have any questions about it. That plus the appendices are ways of, you know, making sure that the patient has whatever information he wants and perhaps information that he should want, even though he might not know it, without sort of bogging it down with wording that's, as people have said, primarily in the interest of lawyers.

**DR. CRONE:** One other thing, though, you may want to take some of what's happening in living donor transplant, some of what they are already considering, and incorporate it, because they are already talking about the fact that you should have a patient advocate. And it could be -- a lot of times that they are having a physician who sees the patient who is not a part of the team. Some places are advocating that as somebody who represents the patient's interest. That really, some of this stuff is already

being done and being written about and, you know, I think that --

In regards to appendices, one of the things I, just to caution, when I'm thinking of just the idea of reading things, appendices, you know, if I'm not really that educated, even being educated are a big -- are a pain, are a real pain, and it just makes it look more and more of a legal document, and I'm kind of wary about how you use appendices.

**MR. BERGER:** I'd just like to add on to what Harold says. It seems to me that this committee has no responsibility for the legal responsibility of the actual institution themselves and we don't even need to worry about it -- I'm not even sure I'd put something in an appendix. You'd might make a statement, but every single medical center that is going to do transplants is going to design their own statements because one of their major concerns of course is to protect themselves. That really shouldn't be ours. We're not doing a turnkey informed statement. And the healthcare institutions can handle their own legal issues, and we should just focus -- and using a patient advocate and other doctor-assisted programs are great, but the legal part, I don't even think we should worry about.

**DR. VANDERPOOL:** Well, when you're on an IRB you have to deal with institutional legal issues. So what we would want to do in this study of procedure section is to say that the IRB and the researchers would need to focus on what patients need to know and consider institutional liabilities as secondary, and certainly to not, to not undermine the process of consent by having such detail in this section that patients really turn off and don't want to read anymore, don't want to understand. So those are the kinds of things we can say that addresses legal issues.

I do think that we can't forget that we have to give doctors their due. The doctors, when they say these are the surgical procedures that we're going to go through, well, you know, you can't say, oh, well, that's mindless detail. I think the physicians are the ones to decide what these tiers of procedure are that need to be explained. And we need to, instead of just merely listing these things out, say that, you know, physicians are the ones who, in their tradition of surgery or whatever, know what procedures need to be specified for the sake of patient understanding, because it takes the patient's through a new risk or a new tier of procedures.

Risk. Organ rejection, immunosuppression is a big one. Risk of infection. The bearing of these risks on patients' behavior, sexual intimate contacts. Statement, these risks will be minimized by precautionary measures under responsibilities. This would be the responsibilities section that follows. Potential for being isolated or quarantined. So the risk of infection for the patient, the risk of transmitting infections to intimate contacts, family and the public, risk of loss confidentiality due to a variety of things, including interest of the media. Any comments about this section on risk? Eda?

**DR. BLOOM:** I think you'll want -- first of all, we have to protect patient confidentiality regardless, but, I mean, that's kind of a regulation, but surely things like this will happen. I think you want to put that the Public Health Service agencies will have access to the records and to specimens collected.

**MS. SHAPIRO:** Also, part of the loss of the confidentiality is getting the intimate contacts involved.

**DR. VANDERPOOL:** Okay.

**DR. COLLINS:** I just have a general question then. In the foundations of my mind informed consent are volunteerism and then confidentiality. Is this whole xenotransplantation stuff so different that those are no longer the cornerstones? Kind of a philosophical question.

**DR. VANDERPOOL:** Volunteerism.

**DR. COLLINS:** That we can still go with, volunteerism.

**DR. VANDERPOOL:** We can go with -- but as you know, when you have desperate patients, the condition is coercive. The pressure is not whether Dr. Collins is saying, hey, you know, you need to get on this protocol, it's that the condition is screaming loudly saying, get the heck on any protocol that they have to present. So, in that sense, you know, severe disease has its own aspects of coercion. So I don't think volunteerism goes, but the disease process may mean it's almost a moot point for desperate patients.

Confidentiality I think is an issue. I think there are other things to add here. The news media is going to be interested. You do have lifelong monitoring. You do have intimate contacts that will be told to give regular samples and to be monitored, explain unforeseen illnesses.

**DR. COLLINS:** Eda brought up a point earlier where she said that, and it's true, you can't -- I mean, unless they consent to the family knowing about all this going on, you can't tell the family -- I mean, if a patient is HIV positive, I can't tell the family that, it's the responsibility of the patient. And I guess is xeno such that they lose that? It's regulation I know.

**DR. BLOOM:** But xeno is, the level of risk with xeno is so much less than the level of risk for HIV.

**DR. COLLINS:** Right.

**DR. BLOOM:** That it would be hard to justify.



**MS. SHAPIRO:** If we include in the consent form we're going to be talking to your family and they sign the consent form, that's kind of like a condition precedent to their getting on board. So they are signing, at least with respect to those people who are intimate contacts at that time, who we know we are going to talk to, I think you can do that.

**DR. COLLINS:** That makes sense.

**DR. VANDERPOOL:** Jon.

**MR. NELSON:** Why do you have item number three there in the loss of confidentiality? I mean, there are lots of procedures that might be of interest to the local media, and that doesn't obligate the transplant program to disclose that information to the media. I don't see why that's even necessary. I mean, fine, what you're saying there is, well, people might find out about it. Well, that's true for anything, but that doesn't necessarily mean that the transplant program can disclose that unless the person is --

**DR. VANDERPOOL:** Absolutely. But we're talking about the risk of loss confidentiality. There is a risk.

**DR. COLLINS:** He's saying that it's going to be --

**DR. VANDERPOOL:** You can minimize a risk, but there is a risk. Keith Rimska (phonetic) wrote a whole article about this, Jon, in which new transplant patients exist. If there's anybody who wants to chase this down, I mean, of all the patients who are going to be chased down, these patients will be. So it's not that it's a loss of confidentiality it's a risk that your confidentiality will be --

**DR. CRONE:** But do you put that in current procedures? Is this sort of statement included in current procedures that tend to bring the interest of media, that's why I'm kind --

**MR. NELSON:** I agree.

**DR. CRONE:** That's my question. That's what I'm trying to say.

**MR. NELSON:** I don't see what that statement adds.

**DR. CRONE:** When patients sign informed consent now, like living donor gets a lot of press now, and I don't know this as being something to put in the informed consent for those people who are --

**MR. NELSON:** If anything, you would put something in the confidentiality that you're protected by whatever prohibitions we have for information disclosure. But you need to be aware that as a procedure which is in the public domain, that people like seeing what's going on, you know, other people might find out. We will not disclose that information but be prepared there might be some press.

**DR. COLLINS:** I think that's exactly the point, Harold, that you're making, the hospital's still going to do its best to comply with the wishes of the patient.

**MR. NELSON:** They are obligated to. I would put the loss confidentiality under -- I know you've got it under risk, but I would put it under the discussion of confidentiality.

**MR. BERGER:** I think, Jon, your point is well taken. I think Harold just needs to change around his wording. It's almost like because of three, you know, that's kind of because of three you have the risk of losing your confidentiality, despite the fact that it's protected, you know. And whether it's here or somewhere else, I just think it's changing that around.

**MR. NELSON:** It looks like on first blush they are going to disclose that information, and that's not the message you want to get across.

**DR. VANDERPOOL:** Okay. Excellent. That's what we're after. We're after changes in wording and suggested changes in place.

The final section I think are pretty straightforward. We've got to go to the process of consent for a while. Number 10 needs to be reworked by Robyn and committee. I just tried to put something in there, and that's going to have to be thoroughly relooked at and we're going to have to find some wording. But I think our question -- outlined in my draft, my question to you, are there other categories here, is this arranged all right? Would you suggest other -- are the topics and subtopics okay? Do these maximize comprehension? These are the things we are trying to do right here. Now, let's move to the process of consent. Robyn, why don't you take over for that?

**MS. SHAPIRO:** Can I just go back to one other thing?

**DR. VANDERPOOL:** Okay.

**MS. SHAPIRO:** One topic that we haven't talked about today anyway, this relates to the participants section. Inclusion and exclusion criteria, and the notion of children and incapacitated adults. We had thought, I think a while back, at the moment these trials should not be open to those people.

**DR. CRONE:** That's what we said in the last meeting, is actually we had said it should be for adults and adults who are capable of comprehending.

**DR. VANDERPOOL:** Maybe two --

**MS. SHAPIRO:** So exclusion criteria would include incapacity?

**DR. VANDERPOOL:** We usually -- yeah, usually inclusion, exclusion criteria have to do more with physiologic status and --

**MS. SHAPIRO:** Where would we put that then if not there, not open to participation our --

**DR. VANDERPOOL:** Well, you might have patients' age, 18 and older, that kind of thing, that would belong here. Exactly.

**DR. COLLINS:** Robyn, I remember that line of conversation. The more I think about it, we may not have time to get to this, but I'll pass it out when we're done. The more I think about it, a lot of certainly parents and a lot of folks would argue that children be included if it's a life-saving procedure. Certainly I know -- I think the FDA has these guidelines, if you possibly can include children in various studies, certainly drug studies and that sort of thing, and I'm wondering if that will elicit -- if we exclude children and folks who are incapacitated, whether that will be too exclusionary, which --

**MS. KING:** Wasn't the rationale for that, and I'm not saying we should stick with that, is because people have to agree for lifelong surveillance, that those people were not capable of giving their own consent to that. Was that not our line of thinking?

**DR. COLLINS:** True.

**MS. SHAPIRO:** Also in the regulation there's general statements that for these kind of populations they need extra special scrutiny about whether this is in their best interest. Without being much more helpful than that the regulations aren't. But the thought that could an incapacitated adult, for example, the burden of a lifelong monitoring, obviously, couldn't be met by that person alone probably.

**DR. COLLINS:** Incapacitated, someone just bring up a clinical example, hepatic coma. Would they be considered incapacitated? It's just temporary because your liver's not getting rid of the toxins and if you got a new liver you would be totally normal.

**MS. SHAPIRO:** And that's the hope we would be able to accomplish with this trial. That's not necessarily going to happen because that's why it's research. We don't know.

**DR. VANDERPOOL:** My assumption in putting inclusion and exclusion criteria in this document, whatever the protocol is, then the protocol needs to say what it is. The question of whether children should be included, whether incompetent patients should be included, whether those who are in coma for a brief period of time, that's really quite another subject I think to be dealt with. Robyn, why don't you deal a little bit with the process of consent?

**MS. SHAPIRO:** Okay. This was not one of my groups but --

**DR. VANDERPOOL:** My usual OCD approach here is to have at least -- I promised Robyn I would do this, so that is have a few notes out. You don't have to look -- go through these. So Robyn why don't you proceed?

**MS. SHAPIRO:** I don't think that make sense, why don't you?

**DR. VANDERPOOL:** No, no, no, you're it.

**MS. SHAPIRO:** It's wonderful that you did this and you should. Go ahead.

**DR. VANDERPOOL:** Okay. The section, as I said, that Lilly and I have done on ethical foundation serves as background process. Robert Levine comments that consent should be understood as a continuing process rather than event symbolized by signing of a form. He characterizes informed consent as a discussion or a negotiation, while Jay Katz envisions consent as a searching conversation.

Process consent therefore involves a continuing exchange of information. It involves enlisting questions, listening to, understanding and evaluating the competency of perspective research subjects, not merely relaying information.

Factors affecting the informed consent process. I'm not knowing where we go with this, but I'm just suggesting some things. The values, religious beliefs, personalities, coping styles, communication styles, age, gender, races, education, cultural background, hearing ability and certainly you should have a physical condition of -- the hearing ability of both researchers and prospective subjects, and the physical condition of the subject.

Researchers need to avoid attempt to control or need to be in control. Recognize degrees to which patient subjects are dependent and shy and researchers need to try and foster mutual trust it.

It's important to ask what the standard for consent should be. Is it an objective standard based on information and language or a reasonable personal standard. One of the favorite phrases within law, or an individual standard that adjusts the consent process,

each prospective subject as a unique individual.

Those are simply some of my thoughts. So what do you think this section ought to be on and what all should we say? The process of informed consent. Lilly. Just proceed as you wish.

**DR. RUSSOW:** I guess that I think what you have here is valuable, at least as a starting point. I mean, we can disagree about some of the points, but it really doesn't describe a process. It sets some criteria for a good process, and obviously you need to have that sort of thing before you actually try to deal with the process, but calling it the process of informed consent is a little bit misleading.

**DR. VANDERPOOL:** I'd be happy to amend -- this was a quickie by me. Notice on the criteria it related to process of informed consent.

**DR. RUSSOW:** Or we could just follow that up with some indications about what kinds of processes might satisfy these criteria better than others, use this as a sort -- the first part, of a description or a section on the process, but follow it up with some recommendations about or at least some comments about what kinds of processes would not meet these criteria and what sorts of choices you have in order to meet those criteria.

**DR. CRONE:** I would think you would want to have -- I agree, Lilly, this doesn't really talk about process. Process, and we talked some about it last time, like the fact that we felt that one of the things you have with informed consent is that you should be doing stepwise, there should be more than one meeting because this is going to be an overwhelming amount of information. You can't just throw a form at somebody, talk to them for an hour, get them signed and that's it. That's part of what I thought of when I thought -- and I had looked at those notes, and I know we had had it written under process. Process to me also includes the talk of do you have a -- some form of patient advocate, some sort of third party, you know, that we believe that things would be advisable.

**MS. KING:** I think we'd also talked not only about education but also assessing understanding as part of that process. The assessment of what they are told.

**DR. VANDERPOOL:** How important, Karren, do we think assessing understanding is for especially patients that are severely compromised? How much --

**MS. KING:** I think if you know they are severely compromised, like a situation you described, you can't assess their understanding because they don't have understanding. But I think of people that are not compromising, most definitely to assess their understanding.

**DR. CRONE:** But that's part of what you can also do in a stepwise process.

**MS. KING:** Exactly.

**DR. CRONE:** Part of what you can do is see what, you know -- you don't throw everything at once, and you see what they can -- each time you can revisit what was talked about before, teach them something new, answer questions, new questions that have come up. It also kind of assesses the commitment of that person, because you know part of what we're -- the other piece is are they really willing to face what they are going to have to face, like the long term monitoring. And part of doing stepwise consent process, it's a little bit of a first step in seeing what they are willing to do. At least that's what they do -- I know with living donor they talk about doing that in stepwise process. Part of that is to see how motivated that donor really is to face the risks that they are going to have to go through if they want to do that. And I think that sort of concept, to me, still holds with xeno.

**MS. KING:** I think it's true, but I think a living donor is a well person or they wouldn't be a living donor. We're talking about individuals in need of this who are probably not physically -- I think we need to do it in steps, but I think we need to look at what types of steps, because we're talking about somebody who is ill and they may not be able physically to handle a lot of demands on them.

**DR. VANDERPOOL:** Jim, I know you and Catherine and Karren were dealing with this issue. Do you have thoughts on process of consent, maybe a better process than the one you had or the same?

**MR. FINN:** Actually, I think they took very good care of me at BU. Everything was carefully explained, nothing was held back, the good and the bad potential. I wasn't pressured at all. The consent form was a bit long, but it was written in Robyn's legalese. So I'd say I was handled well. You have the consent form there, that's Phase II that you've got that I got from the last meeting. Phase I was a little more complex because it was to the efficacy -- it was safety testing, not efficacy testing. But it's basically the same form. I was happy with it. I still have it and that was five and a half years ago. It spells out very carefully about responsibilities such as monitoring and checking with the hospital and all of that, change of address and all that sort of thing. I think it's a good form.

**DR. VANDERPOOL:** A lot of these categories I took off of that form. And you're saying, though, that the form was not as important as the interaction you had with the personnel. Now, was it one person or was it several?

**MR. FINN:** I was dealing with a nurse and a physician and they took very good care

of me. They explained things very carefully. They were with me for every test that I had to go through, they were there. After a day of testing, which believe me, is horrendous for this kind of problem that I had, they were there to support me and answer any questions I might have had. I think the involvement of the physician is very, very important, and he took time to treat me as a human being and not just another number. That had a lot to do with the success of my operation.

**DR. VANDERPOOL:** Of all people, David Trooper and I had some disagreements over this. I argued in one of my articles that physicians ought to do the process. This is before I, you know, learned as much as I have now. And Cooper came back and said, no, the physicians are often too enthusiastic, you need to have someone else, too. So what you're saying confirms one side of my thinking now, and that is it's very important for the physicians to be there, this is not a third-party consent process, this is not a patient advocate who does it all, but this should be -- certainly the physician ought to be included. Are we all agreed on that? Okay.

Other comments from -- and then we've got to break in a minute from -- Catherine or Karren on process? We've covered lots of basis here.

**MR. NELSON:** I have just a question of Catherine since you're so intimately involved with this transplantation. It seems like part of the argument here is to what extent is the surgeon or the attending physician, are they sufficiently removed from the patient, which they are not, to be able to provide independent advice to the patient?

**DR. CRONE:** Yeah.

**MR. NELSON:** And you as a psychiatrist have a different perspective than arguably maybe of -- a different perspective.

**DR. CRONE:** Jon, I think I'm missing the point.

**MR. NELSON:** Is your contention that the physicians are absolutely adequately informed and independent to provide advice to patient?

**DR. CRONE:** Oh, Lord, no. Oh, Lord, no. One of the little things I'm thinking is like -- part of what Jim talks about -- I mean, to hear what treatment you got, your physician and the nurse, they were so involved, which is tremendous, because there are other procedures that are still very new and experimental, so to speak, where you don't get that sort of involvement. I think that may have spoke to those particular individuals, that they -- and part of it is you want to ensure some of that. And I know at least in doing clinical transplant work, one of the things is that we have exposure, patients get exposed to a number of team members. And some of the team members are physicians, such as myself, who kind of probably are people who temper some of the things that are

said or may add in different aspects of things that may be said, depending on who our surgeon is. Not all of them, but we have had people who just, you know --

**DR. COLLINS:** I know what you mean.

**DR. VANDERPOOL:** Why don't we go into the main meeting. We will need at that point to have some of our ideas collected about how long it's going to take us to get something together. But thankful for your being here again with us.

**MR. PHELPS:** Absolutely.

**DR. VANDERPOOL:** How long will it be that we can get our paper together and what should we do with it as we put it together? Jon had some important things to state about that, including --

**MR. PHELPS:** Have you handed out assignments for various pieces of this? Does everybody know what they are responsible for?

**DR. VANDERPOOL:** Yes, we've done that.

**MR. PHELPS:** And did you give them a deadline?

**DR. VANDERPOOL:** We probably will have to go to deadlines next time. We said by the time of this meeting have something to hand out to the group.

**MR. PHELPS:** We got that.

**DR. VANDERPOOL:** Have something to hand out to the group, so that we can take each topic in order and deal with them and begin to put together our document.

**MR. PHELPS:** Do you think by the time of your July meeting that you'll have a draft of the whole paper? I mean, all of the pieces written out that could be circulated beforehand?

**DR. VANDERPOOL:** I think we should. What do other people think? Should we or will we?

**MR. PHELPS:** It's something to shoot for anyhow.

**DR. RUSSOW:** I think we definitely should. But I was just telling Karren that I'm at least -- wasn't clear on what my assignment was. What I got was, you know, can you make some comments on this or, you know, the thing that you said.



**DR. VANDERPOOL:** What happened, you -- Lilly, I tried to call you twice and couldn't get through. Then I sent you this after I spent four or five days working on it. So you and I were sort of out of the loop on connection.

**DR. RUSSOW:** Yeah.

**DR. VANDERPOOL:** For most others we talked about, I wrote to Bradley and Alan and said, okay, we're supposed to be dealing with this consent form content and outline, I'll send you what I've worked up and you give me your comments, and they did that, and I'll work those into this form. And so I think we need to have the same groups actually do a management -- don't you think it makes sense to set a date on between now and our next meeting when each of us has our segment of the paper done?

**DR. RUSSOW:** I guess my question was, I don't know what my segment is exactly.

**DR. VANDERPOOL:** Your and my segment was definition of consent. And then what else were you on? You were on something else.

**DR. RUSSOW:** The process.

**DR. VANDERPOOL:** Process.

**MR. PHELPS:** If I may suggest, Dr. Russow had some very good material to add what was unique about xeno in that initial consent discussion, and that's a very important transition in the paper.

**DR. VANDERPOOL:** Lilly, you and I need to continue to work on the relationship between defining consent and the unique issues in xeno. So you and I need to be responsible for two sections and not -- we don't want to conflate those, but you and I are going to need to do that.

Now, what I think is, not only Lilly and I will do this, but we would get what we've come up with and, you know, Brad and Alan and I will get what we've come up with, which you've already seen. So any of these materials, comment on and get back to me, okay. But then we need to have a draft that is circulated before next meeting so that we can put together a full paper draft, but a full draft by next meeting. Can we agree on that?

**MR. BERGER:** Yes.

**DR. VANDERPOOL:** Okay. I'm not as good as a whip cracker as some people are, but I'll do the best I can.

**MR. PHELPS:** I'll be managing editor for you. I'm just nervous about letting people leave the room without a deadline.

**DR. VANDERPOOL:** Will you take the managing editor role then?

**MR. PHELPS:** Absolutely.

**DR. VANDERPOOL:** You and I will stay in contact with on that.

**MR. PHELPS:** That's what I'm there for.

**MS. KING:** When is our next meeting?

**DR. VANDERPOOL:** Sometime in July, and Mary's not certain which date this will be. Hey, thanks, this has been very productive.

(Breakout session concluded at 12:10 p.m.)